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Rapid and straightforward one-pot expeditious synthesis of 2-amino-5-alkylidene-thiazol-4-ones at room temperature

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ABSTRACT

A new methodology has been developed towards the room temperature synthesis of novel 2-amino-5-alkylidenethiazol-4-ones from aldehydes, amines and rhodanine in one-pot. A heterogeneous dipolar catalyst has been utilized for this reaction. The unique properties of this catalyst effectively synthesize such compounds at room temperature in contrast to all earlier reports.

Thiazolidinone derivatives have been extensively used in drug discovery.[1] They are reported to have anticonvulsant,[2] antibacterial,[3] antiviral[4] and anti-diabetic[5] properties. For example, pioglitazone and rosiglitazone were launched recently for type-II diabetes mellitus. In fact 2-amino-5-alkylidene-thiazol-4-one core is found in more than 15,000 molecules synthesized so far.[6]

Numerous synthetic routes[7–13] have been developed in order to obtain this heterocyclic core. However, the described routes require additional steps with extended reaction times, high temperatures, and laborious work-up all of which are drawbacks of their respective methodologies. Pulici and Quartieri tried to overcome these drawbacks by a traceless two-step solid-phase synthesis[14] that involves reaction of rhodanine with bromo-Wang resin [4-(bromomethyl)phenoxymethyl polystyrene] in DMF under basic condition, followed by a base catalyzed Knoevenagel condensation. Finally an exhaustive piperidine-mediated cleavage in DME–TFE (9:1) followed by silica gel-chromatography led to the recovery of the expected 2-amino-1-yl-thiazol-4-one. Therefore, it still suffers from a rather expensive solid support, additional steps of loading of rhodanine on solid support and cleavage. Bourahla et al. reported an efficient microwave assisted one-pot tandem reaction[15] which employed the aldimine instead of aldehyde. However, it comprises a rather complicated sequence of reaction steps of generation of aldimines, addition of rhodanine followed by the addition of amines and each step requires microwave heating around 80 °C. Additionally the primary amine used for aldimine is completely wasted. In recent years, Anderluh et al. reported an acid catalyzed microwave assisted three component one-pot synthesis of 2-amino-5-alkylidenethiazol-4-ones.[16] However, it requires high temperature (~150 °C) microwave heating which promotes the aromatic aldehydes to undergo competitive Cannizzaro reaction under high temperature and in the presence of excess secondary amine. They used double equivalent of aldehydes for good yield and thus one equivalent is completely wasted. Therefore it is no longer a green methodology.

We thus wish to disclose the development and implementation of a new methodology for the synthesis of 2-amino-5-alkylidenethiazol-4-ones at room temperature. It works well with activated, neutral, hetero-aromatic and electron donating aromatic aldehydes; cyclic and acyclic secondary amines, as well as aliphatic primary amines. Moreover, preparation of these materials at room temperature using greener solvents is a welcome change over the existing methods.

We were particularly interested in the synthesis of 2-amino-5-alkylidenethiazol-4-ones from aldehydes, rhodanine and amines at room temperature. The amine acts as the catalyst in the Knoevenagel condensation and as a nucleophile in the second step and therefore an excess of amine is required. However, use of excess amine is detrimental to the yield.[16] This is because of a competitive Cannizzaro reaction, a typical reaction for aromatic aldehydes in the basic media that yields aromatic acids and consumes aldehydes in the reaction mixture proven by ^{1}H NMR spectra. Also at high temperature and in excess base compound (**1**) is produced as side products.[14a,b] which may arise from the nucleophilic displacement of an alkylidene thiazolone group by means of the anion generated on a second thiazolone moiety. Interestingly the amount of this type of side product depended also on the temperature and

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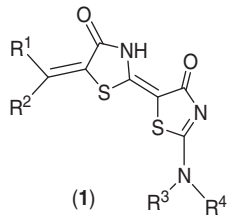
on the strength of the bases: in both cases, the greater the strength, the higher the yield.



(1)

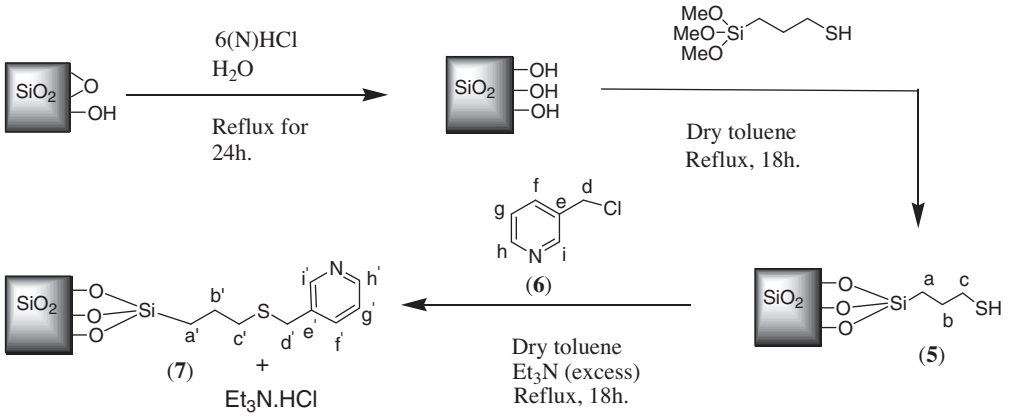
Therefore, use of equivalent amount of amine and low temperature is the ideal condition for good yield and a clean reaction. In that case an additional base catalyst must be used for Knoevenagel condensation and the basicity must be lower than the amines to reduce Cannizzaro reaction and side products (**1**) formation.

The one-pot synthesis was optimized on a model reaction involving 2-bromobenzaldehyde, rhodanine and morpholine under different conditions and the results are summarized in Table 1. The reaction was first tried with 2-bromobenzaldehyde (1 equiv, 0.25 mol/L), rhodanine (1 equiv, 0.25 mol/L), excess (2 equiv, 0.5 mol/L) morpholine in aqueous ethanol for 12 h stirring at room temperature. We isolated only small amount of compound (**2**). However, 20% yield of compound (**3**) was obtained at 5 h under

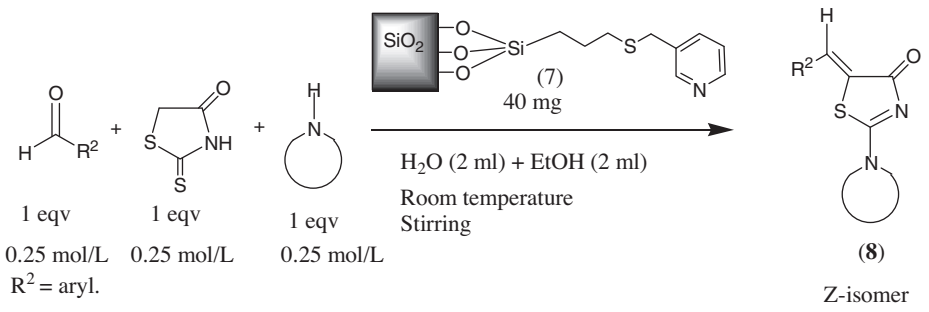
Table 1
Optimization of reaction conditions[a]

Entry	Morpholine (equiv)	Base catalysts (0.1 equiv)	Acid catalysts	Solvents (ml)	Time (min)	Temperature (°C)	Isolated yields (%)
1	2.0	—	—	H_2O+EtOH (2+2)	12 h	30	0
2	2.0	—	—	H_2O+EtOH (2+2)	5 h	80	20
3	2.0	—	AcOH (0.1 equiv)	H_2O+EtOH (2+2)	90	80	47
4	2.0	—	$FeCl_3$ (0.1 equiv)	Dry EtOH (4 ml)	70	75	55
5	2.0	—	Silica (40 mg)	H_2O+EtOH (2+2)	75	30	64
6	1.5	—	Silica (40 mg)	H_2O+EtOH (2+2)	80	30	69
7	1.1	—	Silica (40 mg)	H_2O+EtOH (2+2)	90	30	76
8	1.0	—	Silica (40 mg)	H_2O+EtOH (2+2)	120	80	0
9	1.0	NaOH	Silica (40 mg)	H_2O+EtOH (2+2)	40	30	10
10	1.0	K_2CO_3	Silica (40 mg)	H_2O+EtOH (2+2)	45	30	17
11	1.0	DBU	Silica (40 mg)	H_2O+EtOH (2+2)	50	30	34
12	1.0	Triethyl amine	Silica (40 mg)	H_2O+EtOH (2+2)	52	30	35
13	1.0	DABCO	Silica (40 mg)	H_2O+EtOH (2+2)	80	30	70
14	1.0	2,6-Dimethyl-pyridine	Silica (40 mg)	H_2O+EtOH (2+2)	96	30	81
15	1.0	Pyridine	Silica (40 mg)	H_2O+EtOH (2+2)	100	30	85
16	1.0	Trimethylamine *N*-oxide	Silica (40 mg)	H_2O+EtOH (2+2)	5 h	30	39

[a] Reaction and conditions: rhodanine (1 equiv, 0.25 mol/L), 2-bromobenzaldehyde (1 equiv, 0.25 mol/L), different amounts of morpholine, different acid catalysts, different temperature, stirring.

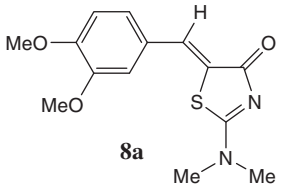
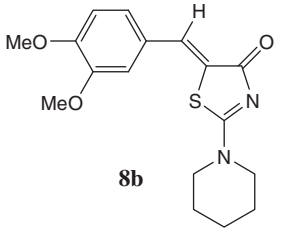
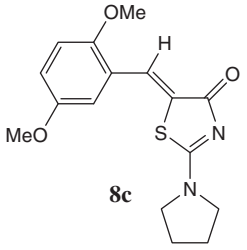
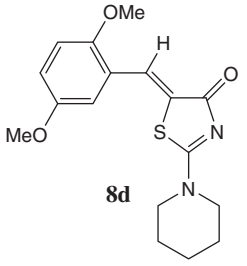
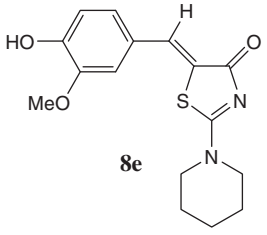
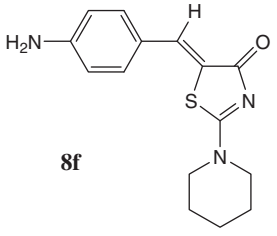
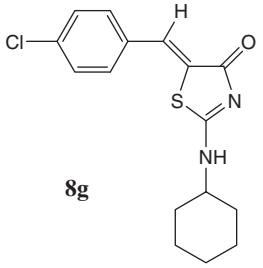


Scheme 1. Preparation of silica based substituted pyridine catalyst.



Scheme 2. Preparation of 2-amino-5-alkylidenethiazol-4-ones.

Table 2
Preparation of 2-amino-5-alkylidenethiazol-4-ones[a]

Entry	Products[b] (numbering)	Time (min)	Melting point (°C)	Isolated yields[c] (%)
1	 **8a**	120	202–204	65
2	 **8b**	122	198–200	79[23]
3	 **8c**	131	212–214	74
4	 **8d**	125	148–150	80[19]
5	 **8e**	139	192–194	83
6	 **8f**	104	212–214	88
7	 **8g**	140	222–224	60

(*continued on next page*)

Table 2 (*continued*)

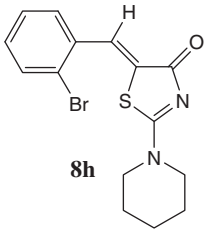
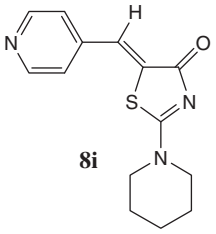
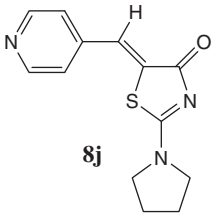
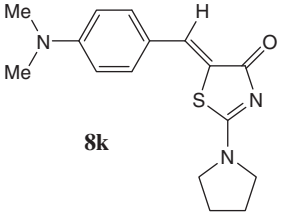
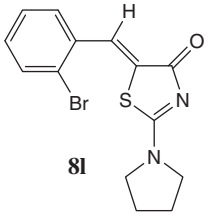
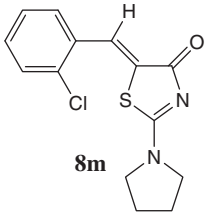
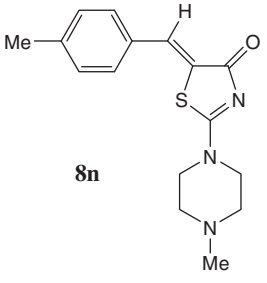
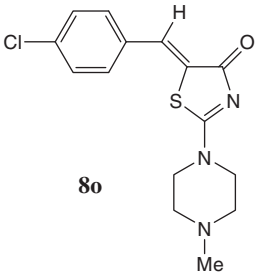
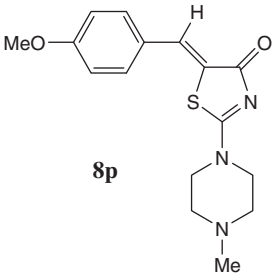
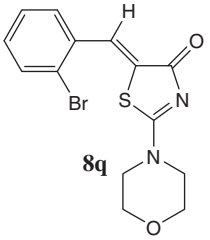
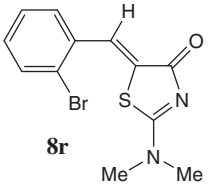
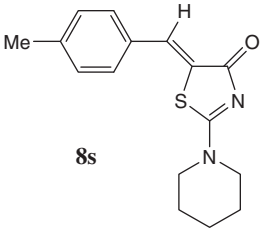
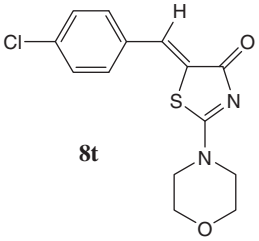
Entry	Products[b] (numbering)	Time (min)	Melting point (°C)	Isolated yields[c] (%)
8	 **8h**	110	162–164	91
9	 **8i**	112	172–174	96
10	 **8j**	110	214–216	80
11	 **8k**	100	228–230	85
12	 **8l**	130	210–212	87
13	 **8m**	128	236–238	85
14	 **8n**	102	222–224	77

Table 2 (*continued*)

Entry	Products[b] (numbering)	Time (min)	Melting point (°C)	Isolated yields[c] (%)
15	 **8o**	95	188–190	81
16	 **8p**	104	172–174	82
17	 **8q**	120	234–236	92
18	 **8r**	100	196–198	65
19	 **8s**	109	152–154	89[22]
20	 **8t**	121	236–238	90[14b]

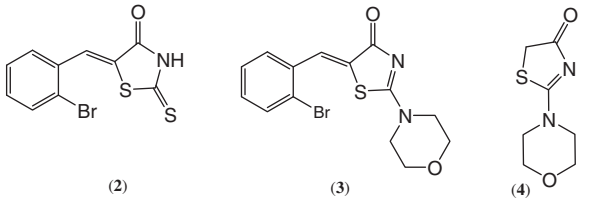
[a] Reaction and conditions: rhodanine (1 equiv, 0.25 mol/L), aldehyde (1 equiv, 0.25 mol/L), amines (1 equiv, 0.25 mol/L), 40 mg silica based substituted pyridine catalyst (**7**), aqueous ethanol [(2+2) ml], room temperature, stirring.

[b] The *Z*-diastereoselectivity is conformed by X-ray single crystal analysis of (**8t**) (entry 20).

[c] References.

refluxing condition. Interestingly the yield increased to 47% in 90 min with AcOH as an additional acid catalyst. Therefore, condensation of rhodanine with amine is catalyzed by an acid. This step was catalyzed also by different Lewis acids with an overall yield of 40–55% under refluxing condition. However, maximum of 64% yield was attained within 75 min at room temperature when silica was used as an acid catalyst. Here the silanol groups present on the silica surface coordinate with the carbonyl oxygen to increase its electrophilicity[17,18] and thereby reduces the time of Knoevenagel reaction and temperature. Therefore, under low

temperature and in reduced reaction time the extent of Cannizzaro reaction and side product (**1**) formation is reduced. Decreasing the amount of morpholine to 1.1 equiv in the presence of silica catalyst increased the yield to 76% because of further decrease in the side product formation under limited supply of amines.



However, when we used 1 equiv of each of rhodanine, aldehyde and morpholine, in the presence of silica as Bronsted acid catalyst, we isolated mainly the compound (**4**) and unreacted aldehyde.

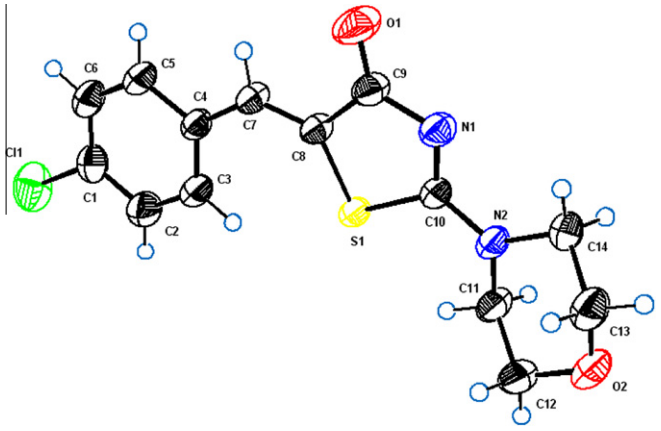


Figure 1. ORTEP diagram of single crystal obtained from 5-(4-chloro-benzylidene)-2-morpholine-1-yl-thiazol-4-one, (**8t**) showing the crystallographic numbering (CCDC 836806).

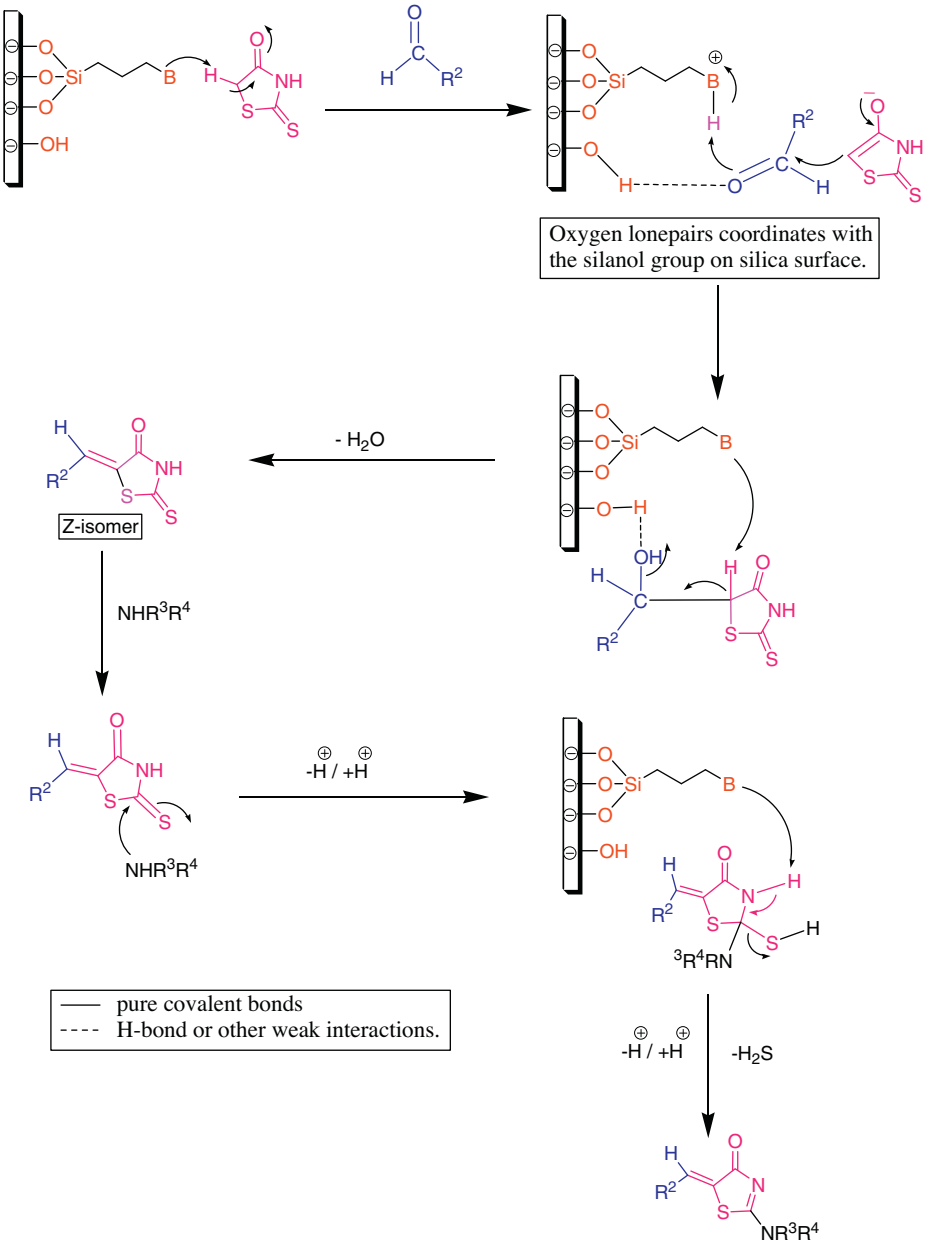


Figure 2. Mechanism of preparation of 2-amino-5-alkylidenethiazol-4-ones.

Therefore, condensation of rhodanine with aldehydes needed a base catalyst, particularly when equivalent amounts of rhodanine, aldehyde and morpholine were used. Therefore, reagent quantity is optimized as 1 equiv of each of the amine, rhodanine and aldehyde. In that case the use of a weak base catalyst and silica as a Bronsted acid catalyst represents the most powerful methodology for room temperature preparation of 2-amino-5-alkylidenethiazol-4-ones. The yield decreased substantially when NaOH was used as a base catalyst. Decreasing the base strength increased the yield probably due to the minimization of side products with weaker base catalyst though with higher reaction time. Pyridine as a base gave maximum yield. Further decrease in base strength resulted in incomplete conversion.

However, pyridine is potentially harmful to the experimentalist. Therefore, we have designed and synthesized the following bifunctional silica-based substituted pyridine catalyst (**7**) according to Scheme 1 to avoid this harmful effect of pyridine.

Here 2-chloromethylpyridine provides straightforward possibilities for catalyst design, together with a simple immobilization procedure compared to other less- functionalized organocatalysts.

Using this catalyst a variety of 2-amino-5-alkylidenethiazol-4-ones were synthesized from rhodanine (1 equiv, 0.25 mol/L), amines (1 equiv, 0.25 mol/L), and a variety of aldehydes (1 equiv, 0.25 mol/L) according to Scheme 2. The products (Table 2) obtained in excellent yields and were highly pure.

In all cases, the ^{1}H NMR spectra revealed only one type of methine proton which ensured the formation of only one type of geometrical isomer and the *Z*-diastereochemistry was confirmed by X-ray single crystal analysis (Fig. 1) of 5-(4-chloro-benzylidene)-2-morpholine-1-yl-thiazol-4-one, (**8t**) (Table 2, entry 20) (CCDC 836806).

Mechanism

Here Knoevenagel condensation preceded the condensation of rhodanine with amine as confirmed from the ^{1}H NMR spectra of the isolated product obtained by quenching the reaction after few minutes. The quenching was done by simply removing the catalyst from the reaction mixture through filtration. The starting organic compounds remain in the homogeneous phase of aqueous-ethanol. Since the catalyst is heterogeneous, it is outside the homogeneous phase.[18] Water forms several hydrogen bonds between the nitrogen atom of catalyst (**7**) and the organic molecules, thereby acting as a bridge between the homogeneous and heterogeneous phases.[18] Here water brings the active methylene groups to the lone pair of electrons of pyridine nitrogen of the catalyst through hydrogen-bonding (Fig. 2) and thereby favouring the ionization into carbanion donor.[18,20,21] The carbonyl oxygen coordinates with the silanol[17,18]groups on silica surface increasing the electrophilicity of the carbonyl carbon and thereby making it possible to carry out the reaction at room temperature and in short time (Fig. 2).

Study on optimization of catalyst loading and choice of solvent

To study the effect of catalyst loading the reaction of rhodanine with 2-bromobenzaldehyde and pyrrolidine was chosen as the model reaction. The results show clearly that the silica based substituted pyridine (**7**) is an effective catalyst for this transformation and 40 mg of the catalyst was the optimum usage under this condition and the yields did not increase largely with higher amount of catalyst. It should be noted that, the yield was best with EtOH–water [(2+2) mL]. The yield decreased substantially when the reaction was conducted in less polar solvents, such as CH_2Cl_2, ACN, THF etc., (Optimization table in Supplementary data).

Recycling experiment

The possibility of recycling the catalyst was examined using the reaction of rhodanine with 2-bromobenzaldehyde and pyrrolidine under optimized conditions. The recycled catalyst could be used at least eight times without any further treatment. A negligible loss in the catalytic activity of silica based substituted pyridine catalyst was observed (Recycling table in Supplementary data). The slightly extended time for the recycles is probably due to the loss of some amount of catalyst in the time of filtration.

In conclusion we have developed a rather novel protocol[23] for the one-pot three-component synthesis of 2-amino-5-alkylidenethiazol-4-ones from rhodanine, amines and aldehyde in room temperature in contrast to all the earlier reported methods where high temperature was required. It represents a powerfully green technology procedure for the use of environmental friendly solvent and prevention of unwanted waste production. Shorter reaction times and one pot strategy make it convenient for parallel synthesis.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.09.090.

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23. General experimental procedure for the synthesis of 2-amino-5-alkylidenethiazol-4-ones: A mixture of rhodanine (0.25 mol/L), amine (0.25 mol/L), and ketone (0.25 mol/L) and 40 mg of silica based substituted pyridine catalyst in aqueous ethanol [(2+2) ml] were stirred in room temperature until the reaction is completed. The completion of the reaction was indicated by the disappearance of the starting material in thin layer chromatography. The products precipitated out once their formation started. After completion of the reaction the crude product was filtered and the residue was taken in DCM. It was again filtered to separate the product as filtrate from the catalyst which is separated as residue. It was further purified either by recrystallization from EtOAc/DCM (equal volume).